

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Smith et al.)	Group Art Unit:	unknown
)	(Parent:	1653)
Serial No.:	unknown (Divisional of)		
	Serial No.: 09/070,504))	Examiner:	unknown
)	(Parent:	A. M. Davenport)
Filed:	herewith)		
For:	PEPTIDE ANTAGONISTS OF CGRP-RECEPTOR SUPERFAMILY AND METHODS OF USE			

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

Sir:

Prior to taking up the above-identified divisional patent application for examination, please amend the application as follows:

In the Specification

Please insert the following new paragraph at page 1, line 4 (immediately before the "Field of the Invention" heading) as instructed in the Request for Filing a Divisional Patent Application filed herewith:

-- This is a divisional application of Serial No. 09/070,504, filed April 30, 1998 (pending), which is incorporated herein by reference. --

Please replace the paragraph beginning at page 1, line 11 with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A (attached herewith) with notations to show the changes made.

-- The calcitonin gene related peptide (CGRP) is a sensory neuropeptide with potent vasodilatory and cardiotonic action as described in U.S. Pat. No. 4,530,838 to Evans et al. The peptide exists in two forms (denoted α and β). α -CGRP is produced by the calcitonin gene (Amara et al. *Nature* 298:240-244, 1982 and Rosenfeld et al. *Nature* 304:129-135, 1983) while

β -CGRP is the product of a separate gene (Amara et al. *Nature* 298:240-244, 1985 and Steenbergh et al. *FEBS Lett.* 183:403-407, 1982). The human β -form and α -form differ by three amino acids. --

Please replace the paragraph beginning at page 1, line 27 with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to show the changes made.

-- The release of CGRP from sensory nerve endings in inflammatory reactions can result in the local acceleration of microhemodynamic changes including vasodilation and permeability of the microcirculation resulting in plasma exudation and the release of humoral factors and inflammatory cells to the site of injury. CGRP has been used as a vasodilator in animal models of subarachnoid hemorrhage and in trials involving human subjects with congestive heart failure. CGRP administration produced hypotension associated with moderate tachycardia in hypertensive humans (Jian et al. *Chin. Med. J.* 102:897-901, 1989). CGRP has also been used as a potent dilator of the coronary circulation (Ezra et al., *Eur. J. Pharmacol.*, 1987). In contrast to nitrates, which have also been used as vasodilators, CGRP results in dilation by both endothelium-dependent and endothelium-independent mechanisms. Also, in contrast to nitrates, such as sodium nitroprusside, tolerance to CGRP has not been noted Bény et al. *Regul. Pept.* 25:25-36, 1989). CGRP has been demonstrated to improve the ability of patients to participate in exercise programs in patients with chronic stable angina (Uren et al. *Cardiovasc. Res.* 27:1477-1481, 1993). --

Please replace the paragraph beginning at page 3, line 27 with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to show the changes made.

-- CGRP antagonists includes peptides from CGRP including amino acids 8-37 of β -CGRP (Park et al. *Am. J. Physiol.* 1989) having the amino acid sequence:
THRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:1) and peptides from α -CGRP including amino acids 8-37 and having the amino acid sequence

THRLAGLLSRSGGMVKSNFVVPTNVGSKAF. β -CGRP(8-37) (SEQ ID NO:2) has been used to counteract the effects of CGRP. For example, CGRP(8-37) has been shown to reverse the hypotension and tachycardia produced by administration of LPS to rats (Huttemeir, et al. *Am. J. Physiol.* 265:H767-H769, 1993). In addition, CGRP(8-37) has some activity against amylin (Gardiner et al. *Diabetes* 40:948-951, 1991). The affinity for CGRP(8-37) varies between tissues. For example, data indicates that the affinity of CGRP(8-37) for mesenteric artery, kidney, heart and skeletal muscle is somewhat higher than the affinity of CGRP(8-37) for adipocytes and descending colon (Poyner, D. *Trends in Pharm. Sci.* 16:424-428, 1995). --

Please replace the paragraph beginning at page 10, line 15 with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to show the changes made.

-- Preferred adrenomedullin-derived antagonists include:

h-adrenomedullin (22-52) (SEQ ID NO:23)

(TVQKLAHQIYQFTDKDKDNVAPRSKISPQGY-NH₂ Eguchi et al. *Endocrinol.* 135:2454-2458, 1994 and Champion et al. *Am. J. Physiol.* 272:R234-242, 1997). --

In the Claims

Please cancel claims 1-20, 27 and 28, without prejudice and amend claims 21 and 22. The amended claims are provided below in clean form. In accordance with 37 C.F.R. §1.121, amended claims are also shown in Appendix A with notations to indicate changes made.

21. (AMENDED) The method of Claim 29 wherein the CGRP receptor is on a cell.
22. (AMENDED) The method of Claim 29 wherein the CGRP receptor is cell free.

Preliminary Amendment

Page 4

Applicant: Derek D. Smith et al.

Serial No.: unknown (parent: 09/070,504)

Title: PEPTIDE ANTAGONISTS OF CGRP-RECEPTOR SUPERFAMILY AND METHODS OF USE

REMARKS

Claims 1-20, 27 and 28 are canceled without prejudice or disclaimer and claims 21 and 22 are amended. The currently pending claims are 21-26 and 29-53.

The specification is amended to add a cross reference to the prior application and correct typographical errors in the specification.

Applicants respectfully request that the Preliminary Amendment described herein be entered into the record prior to examination and consideration of the above-identified divisional application.

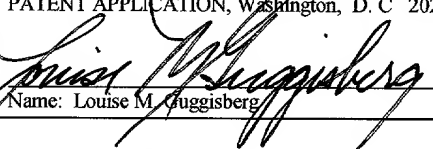
If the Examiner wishes to discuss any issues concerning this communication by telephone, please contact the below-signed attorney at (612) 305-1217.

If any additional fees are deemed necessary in this instance, please charge Deposit Account No. 13-4895.

CERTIFICATE UNDER 37 C.F.R. 1.10:

Express Mail label number EL776900604US
Date of Deposit March 20, 2001

I hereby certify that this paper and/or fee is/are being deposited with the United States Postal Service Express Mail Post Office to Addressee service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Attn: Box PATENT APPLICATION, Washington, D. C. 20231.


Name: Louise M. Guggisberg


March 20, 2001

Date

AMM:lmg

Respectfully submitted,
Derek D. SMITH et al.
By their Representatives,
Muetting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612)305-1220
Facsimile: (612)305-1228

By:


Ann M. Muetting
Reg. No. 33,977
Direct Dial (612)305-1217

**APPENDIX A: Specification/Claim Amendments Including
Notations to Indicate Changes Made**

Title: PEPTIDE ANTAGONISTS OF CGRP-RECEPTOR SUPERFAMILY AND METHODS OF USE
Applicant: Derek D. Smith et al.
Serial No.: unknown (parent: 09/070,504)
Filed: herewith

In the Specification

The following new paragraph has been inserted at page 1, line 4:

Continuing Data

This is a divisional application of Serial No. 09/070,504, filed April 30, 1998 (pending), which is incorporated herein by reference.

The paragraph beginning at page 1, line 11, has been amended as follows:

The calcitonin gene related peptide (CGRP) is a sensory neuropeptide with potent vasodilatory and cardiotonic action as described in U.S. Pat. No. 4,530,838 to Evans et al. The peptide exists in two forms (denoted α and β). α -CGRP is produced by the calcitonin gene (Amara et al. *Nature* 298:240-244, 1982 and Rosenfeld et al. *Nature* 304:129-135, 1983) while β -CGRP is the product of a separate gene (Amara et al. *Nature* 298:240-244, 1985 and Steenbergh et al. *FEBS Lett.* 183:403-407, [1985] 1982). The human β -form and α -form differ by three amino acids.

The paragraph beginning at page 1, line 27, has been amended as follows:

The release of CGRP from sensory nerve endings in inflammatory reactions can result in the local acceleration of microhemodynamic changes including vasodilation and permeability of the microcirculation resulting in plasma exudation and the release of humoral factors and inflammatory cells to the site of injury. CGRP has been used as a vasodilator in animal models of subarachnoid hemorrhage and in trials involving human subjects with congestive heart failure. CGRP administration produced hypotension associated with moderate tachycardia in hypertensive humans (Jian et al. *Chin. Med. J.* 102:897-901, 1989). CGRP has also been used as a potent dilator of the coronary circulation (Ezra et al., *Eur. J. Pharmacol.*, 1987). In contrast to

**APPENDIX A: Specification/Claim Amendments Including
Notations to Indicate Changes Made**

Title: PEPTIDE ANTAGONISTS OF CGRP-RECEPTOR SUPERFAMILY AND METHODS OF USE
Applicant: Derek D. Smith et al.
Serial No.: unknown (parent: 09/070,504)
Filed: herewith

nitrates, which have also been used as vasodilators, CGRP results in dilation by both endothelium-dependent and endothelium-independent mechanisms. Also, in contrast to nitrates, such as sodium nitroprusside, tolerance to CGRP has not been noted ([Foulkes] Bény et al. *Regul. Pept.* 25:25-36, 1989). CGRP has been demonstrated to improve the ability of patients to participate in exercise programs in patients with chronic stable angina (Uren et al. *Cardiovasc. Res.* 27:1477-1481, 1993).

The paragraph beginning at page 3, line 27, has been amended as follows:

CGRP antagonists includes peptides from CGRP including amino acids 8-37 of β -CGRP ([Chiba] Park et al. *Am. J. Physiol.* 1989) having the amino acid sequence: THRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:1) and peptides from α -CGRP including amino acids 8-37 and having the amino acid sequence THRLAGLLSRSGGMVKSNFVPTNVGSKAF. β -CGRP(8-37) (SEQ ID NO:2) has been used to counteract the effects of CGRP. For example, CGRP(8-37) has been shown to reverse the hypotension and tachycardia produced by administration of LPS to rats (Huttemeir, et al. *Am. J. Physiol.* 265:H767-H769, 1993). In addition, CGRP(8-37) has some activity against amylin (Gardiner et al. *Diabetes* 40:948-951, 1991). The affinity for CGRP(8-37) varies between tissues. For example, data indicates that the affinity of CGRP(8-37) for mesenteric artery, kidney, heart and skeletal muscle is somewhat higher than the affinity of CGRP(8-37) for adipocytes and descending colon (Poyner, D. *Trends in Pharm. Sci.* 16:424-428, 1995).

**APPENDIX A: Specification/Claim Amendments Including
Notations to Indicate Changes Made**

Title: PEPTIDE ANTAGONISTS OF CGRP-RECEPTOR SUPERFAMILY AND METHODS OF USE
Applicant: Derek D. Smith et al.
Serial No.: unknown (parent: 09/070,504)
Filed: herewith

The paragraph beginning at page 10, line 15, has been amended as follows:

Preferred adrenomedullin-derived antagonists include:

h-adrenomedullin (22-52) (SEQ ID NO:23)

(TVQKLAHQIYQFTDKDKDNVAPRSKISPQGY-NH₂ [Watanabe,] Eguchi et al.

[Endocrinol.] Endocrinol. 135:2454-2458, 1994 and Champion et al. *Am. J. Physiol.* 272:R234-242, 1997)[,] .

In the Claims

21. (AMENDED) The method of Claim [20] 29 wherein the CGRP receptor is on a cell.
22. (AMENDED) The method of Claim [20] 29 wherein the CGRP receptor is cell free.